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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,158	09/15/2003	Frederic DeSauvage	11669.123USC1	4053

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EXAMINER
SKELDING, ZACHARY S

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,158	DESAUVAGE ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007 and 05 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 35-68* is/are pending in the application.

4a) Of the above claim(s) *1,36-48,51-56 and 60-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,49,50 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of species of April 23, 2007 is acknowledged.

Claims 1 and 35-68 are pending.

Claims 35, 49, 50 and 57-59 are under examination as they read on a method for inhibiting the differentiation of Th0 cells into a Th2 subtype comprising administering an anti-TCCR antibody agonist wherein said antibody binds the species of TCCR that is "human TCCR".

Claims 1, 36-48, 51-56 and 60-68 are withdrawn as being drawn to a non-elected invention.

2. The previous rejections of record can be found in the Office Action mailed July 5, 2006.

This Office Action is in response to Applicant's election of species filed April 23, 2007 as well as applicant's after final amendment filed January 5, 2007.

The text of those sections of Title 35 U.S.C. not included in this Office Action can be found in a previous Office Action.

The previous rejections under 35 U.S.C. § 112, 1st paragraph have been withdrawn upon further consideration and in view of applicant's argument.

The previous rejection under 35 U.S.C. § 112, 1st paragraph, written description has been withdrawn in view of applicant's amendment to the claims.

Each of the rejections set forth below is a New Grounds of Rejection.

3. Claims 35, 49, 50 and 57-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. A method comprising administering TCCR agonistic antibody *that includes antibodies to TCCR variants*: Claim 49, and dependent claims thereof.

Claim 49, and dependent claims thereof, recite a method comprising administering a "TCCR agonist antibody".

According to the instant specification the term "TCCR" encompasses TCCR variants such as sequences of ≥80% identity to full length TCCR as defined by SEQ ID NO:1 (see instant specification page 14, last paragraph to page 15, last paragraph).

Therefore, the instant claims, given their broadest reasonable interpretation consistent with the instant specification, read on methods comprising the administration of antibodies that bind everything ***from*** SEQ ID NO:1 ***to a protein 80% identical to SEQ ID NO: 1***.

However, in order to be ***useful*** for the claimed method, the anti-TCCR antibodies must recognize TCCR as it occurs in a patient, e.g.., the instant specification discloses one specific native human TCCR sequence, SEQ ID NO: 1 (see page 15, 1st paragraph).

However, there is ***insufficient nexus*** between antibodies which bind a TCCR variant with ≥80% identity to SEQ ID NO:1 **AND** antibodies which bind the specific native human TCCR sequence, SEQ ID NO: 1.

More particularly, the instant specification does not provide sufficient direction or guidance for the skilled artisan to know which particular TCCR ***variants are capable of*** generating antibodies that are able to agonize both the TCCR variant **AND** SEQ ID NO: 1.

In particular is known by the skilled artisan that even "naturally occurring" alleles of TCCR as defined by SEQ ID NO: 1 could be differentially recognized by a given antibody. For example, as shown for CD4 by Lederman et al. (Molecular Immunology 28: 1171-1181, 1991). Lederman describes that while human CD4 is relatively non-polymorphic protein, a single amino acid substitution present in a common CD4 allele ablated the binding of an anti-CD4 monoclonal antibody (see entire document).

Moreover, one of ordinary skill in the art would ***not*** be able to predict which particular amino acid changes in a TCCR variant with ≥80% identity to SEQ ID NO:1 would affect the ability of an antibody generated against the mutant protein to recognize the naturally occurring form.

For example, as illustrated by Colman et al. (Research in Immunology, 1994; 145(1): 33-36) even single amino acid changes in an antigen can effectively abolish antibody-antigen binding (see entire document, particularly page 34). Moreover, Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding (see entire document, particularly Results on pages 435-436).

Thus, the instant claims encompass in their breadth making antibodies to a multitude of polypeptides for which it is difficult to predict which mutation(s) will result in an antigen that will generate an antibody that will, in turn, bind native TCCR as it is found in a patient, e.g., TCCR as defined by SEQ ID NO: 1. Without sufficient guidance or direction for which amino acid sequences and which mutation(s) can be tolerated in the structure of TCCR, while still retaining the structure necessary to generate an antibody that will recognize TCCR as it is found in a patient to be administered agonistic TCCR antibodies, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In conclusion, the instant specification provides insufficient direction or guidance regarding how to practice the instantly claimed method to its full breadth.

Accordingly, undue experimentation would be required to produce the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant is invited to claim the agonistic antibody with reference to a particular sequence found in a patient to be treated, e.g., a TCCR agonist antibody wherein TCCR is SEQ ID NO: 1.

It is noted that claim 35 is included in this rejection because, when given its broadest reasonable interpretation consistent with the instant specification, it reads on antibodies that recognize ***both*** TCCR variants with ≥80% identity to SEQ ID NO:1 and SEQ ID NO: 1, per se; however the as put forth above, undue experimentation would be required to generate such antibodies.

B. Monovalent TCCR agonist antibodies: Claim 49, and dependent claims thereof.

Claim 49, and dependent claims thereof, are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for any method of treatment comprising administration of a monovalent antibody fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The art teaches that antibodies capable of simultaneously binding at least two cytokine receptor molecules or subunits can be agonistic; however, monovalent ligands, such as Fab fragments, are generally inactive in this regard (see Heldin et al., Cell. 1995 Jan 27;80(2):213-23, entire document, in particular page 219, 1st paragraph). Thus, the skilled artisan, as of applicant's date of invention, appreciated that intact antibodies, and divalent fragments thereof, can act as agonists of cytokine receptors by crosslinking receptor molecules. In contrast, antibody fragment with a single antigen binding site, such as the Fab, Fab', F(ab') or Fv were well known to the skilled artisan to generally not be capable of agonizing cytokine receptors.

Likewise, the phrase "single chain antibody" given its broadest reasonable interpretation consistent with the instant specification encompasses monovalent single chain antibodies (see page 31, 1st paragraph of the instant specification) which also would not be expected by the skilled artisan to be capable of agonizing a cytokine receptor. Therefore, development of a method that requires use of such a fragment would require undue experimentation on the part of the skilled artisan.

In conclusion, the instant specification provides insufficient direction or guidance regarding how to make the TCCR agonist antibodies encompassed by the breadth of the instant claims.

Accordingly, undue experimentation would be required to produce the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

   A person shall be entitled to a patent unless –

   (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 35, 49, 50, and 57 are rejected under 35 U.S.C. 102(b) as anticipated by Baumgartner et al. (U.S. Patent No. 5,792,850, cited by applicant)(see entire document) as evidenced by the instant specification at page 3, 1st paragraph, the paragraph bridging pages 4 and 5 and Figure 1, and page 11, 3rd paragraph.

   Baumgartner teaches a Zcytor1 polypeptide (Baumgartner SEQ ID NO: 5) which is 100% identical to TCCR as defined by SEQ ID NO: 1 of the instant application (see SCORE, Genseq result 1). According to Baumgartner (emphasis added), "***[a]gonist ligands for Zcytor1*** may be useful in ***stimulating cell-mediated immunity*** and for stimulating lymphocyte proliferation, ***such as in the treatment of infections involving immunosuppression, including certain viral infections***." (see, in particular, column 15, 1st paragraph). Baumgartner further teaches agonistic ligand of Zcyotr1 include divalent antibodies, and Baumgartner teaches making divalent antibodies including $F(ab')_2$ antibodies. (see, in particular, column 17, 2nd paragraph).

   In addition, Baumgartner teaches that (emphasis added), "the tissue specificity of Zcytor1 expression ***suggests a role in early thymocyte development*** and immune response regulation. These processes ***involve stimulation of cell proliferation and differentiation in response to the binding of one or more cytokines*** to their cognate receptors," and that Zcytor1 is a member of the receptor subfamily including IL-6, LIF, IL-11 and OSM (see, in particular, column 14, column 4, 3rd paragraph and column 5, 3rd paragraph).

It is noted that the instant claims recite "a method of inhibiting or attenuating differentiation of Th0 cells into a Th2 subtype comprising administering..." According to the instant specification, by inhibiting Th2 differentiation the skilled artisan is inherently causing Th1 differentiation, which is useful for treating Th2 mediated disorder characterized by the overproduction of Th2 cytokines such as for treating patients with "exacerbation of infection with infectious diseases" (see paragraph bridging pages 4 and 5 and page 11, 3rd paragraph).

Thus, Baumgartner teaches agonist ligands of Zcytor1 may be useful in stimulating cell-mediated immunity and for stimulating lymphocyte proliferation, such as in the treatment of infections involving immunosuppression, including certain viral infections. Moreover, as evidenced by the instant specification, the instant claims read on a method comprising administering TCCR agonist antibody to promote the formation of Th1 cells over Th2 cells, thereby stimulating cell mediated immunity (see, in particular, page 3, 1st paragraph, the paragraph bridging pages 4 and 5 and Figure 1). As further evidenced by the instant specification, methods that promote Th1 cells in favor of Th2 cells are useful in treating infectious disease, including, for example, human immunodeficiency virus (see, in particular, the paragraph bridging pages 4 and 5).

Thus, Baumgartner's teachings about using agonistic Zcytor1 antibodies to treat infections involving immunosuppression, including certain viral infections, anticipate the instant claims.

Accordingly, claims 35, 49, 50, and 57 are anticipated by Baumgartner.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 35, 49, 50 and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baumgartner et al. (U.S. Patent No. 5,792,850) in view of Queen et al. (US 5,585,089) and Holliger et al. (U.S. Patent No. 5,837,242).

The teachings of Baumgartner are given above.

The instant claim differ from Baumgartner in that Baumgartner does not explicitly teach humanized anti-TCCR antibodies or anti-TCCR diabodies.

However, Queen teaches how to make humanized antibodies. Queen further teaches that humanized antibodies are advantageous because they more closely resemble human

antibodies than do antibodies produced from murine hybridomas and thus have lower immunogenicity and a longer half-life. (see entire document, in particular, column 1).

Moreover, Holliger teaches that bivalent antibody fragments, such as diabodies, are useful because they are smaller in size than other bivalent antibody fragments, such as F(ab')2 fragments, and therefore have greater ability to penetrate tissues than do F(ab')2 fragments (see, in particular, column 13, 4th paragraph).

Given the reference teachings, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art also would have been motivated to apply the humanization techniques of Queen to the agonistic antibodies of Baumgartner since, as has been long appreciated by the ordinary artisan, antibodies are generally administered by injection in a physicians office, and thus patients and their physicians greatly desire antibodies with a long serum half-life and low immunogenicity so as to decrease office visits and patient expense.

Moreover, further given the tissue penetrating advantage of diabody as taught by Holliger, it would have been obvious to one of ordinary skill in the art to prepare anti-TCCR diabody. Also, given that the diabody and F(ab')2 fragments, apart from their structural differences, have art recognized equivalence for the same purpose, i.e., these fragments are both recognized by the art as being possible therapeutic antibody formats as shown by Holliger, it would have been obvious to one of ordinary skill in the art to make anti-TCCR diabody that could be used like the anti-TCCR F(ab')2 of Baumgartner. See MPEP § 2144.06.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

Thus, claim 49, and dependent claims thereof, are unpatentable over Baumgartner in view of Queen and Holliger.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claim 49, and dependent claims thereof, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 20, 23, 24 and 35-39 of copending Application No. 10/088,950.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of 10/088,950 anticipate the instant claims. In particular, while the claims of the reference application recite a method of treating an allergic disorder with anti-TCCR agonist, according to the instant specification allergic disorders are one type of disorder treated by a method of inducing Th1 differentiation with an anti-TCCR agonist.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
July 5, 2007

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7/4/07